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Acute and Chronic Effects of Cisplatin Therapy on Renal Magnesium Homeostasis

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Although the acute renal toxicity of cisplatin has been well documented, long-term follow-up studies in cisplatin-treated children are scanty. We have evaluated the incidence and characteristics of both acute and chronic nephrotoxicity in 22 children (median age 8 years) treated with cisplatin as part of different chemotherapeutic protocols. All patients exhibited a significant and progressive decrease in plasma magnesium (Mg) values soon after cisplatin administration. Magnesiuria also increased immediately after therapy. Hypomagnesemia (plasma Mg <1.4 mg/dl) occurred in 10 patients and it was dose-dependent. Minimal and mean cumulated doses inducing hypomagnesemia were 300 and 500 mg/m^2, respectively. In 18 children we followed renal function prospectively for a mean time of 2.3 years after arrest of cisplatin therapy. Chronic hypomagnesemia and moderate elevation of plasma creatinine were observed in 6 children, hypocalciuria in 5 children, and hypokalemia in 1 child. Presence of hypomagnesemia was unrelated to the total dose received or the time elapsed since cisplatin therapy. Renal function studies, performed in the 6 children with chronic hypomagnesemia, revealed different degrees of impairment in Mg reabsorption. The functional characteristics of chronic cisplatin nephrotoxicity found in the present series—contrary to prior reports—are not comparable to those present in the inherited Gitelman's syndrome.

Key words: cisplatin, nephrotoxicity, magnesium, hypomagnesemia, hypocalciuria

INTRODUCTION

Cisplatin (*cis*-diamminedichloroplatinum or CDDP) is a chemotherapeutic drug with well-known nephrotoxicity [1–3]. This toxicity includes a characteristic renal magnesium (Mg) wasting which can be manifested either acutely [4–9] or chronically after complete arrest of therapy [10–13]. Hypomagnesemia has been recognized as a frequent complication of cisplatin therapy since the first descriptions of Hill et al. [14] in 1978 and Schilsky and Anderson [15] in 1979.

Only a few authors have examined the nephrotoxic effects of cisplatin therapy in children [16–20], and there are no studies about the effect upon renal tubular reabsorption of Mg. The present investigation was designed to better characterize the Mg-losing nephropathy, and especially the persistent abnormalities of renal Mg reabsorption, present in children after withdrawal of cisplatin therapy.

PATIENTS AND METHODS

Patients

The study population consisted of 22 children (12 males, 10 females; age: 1.2–16 years, median age 8 years) treated with cisplatin during the period 1986–1992. Seven patients underwent treatment for neuroblastoma, 4 patients for meduloblastoma, 3 patients for malign teratoma, 2 patients for rabdomyosarcoma, and 1 patient for each of the following tumors: fibrosarcoma, osteosarcoma, choroid plexus carcinoma, germ cell tumor, hepatoblastoma, and diffuse brain glyomatosis. They received a total mean dose of 570 mg/m^2 body surface area (b.s.a.) of cisplatin (range 270–870 mg/m^2 b.s.a.), which was given according to different international chemotherapeutic protocols. Eleven children were surgically treated and 4 received local radiotherapy before the administration of cisplatin.

Preceding each cisplatin dose all children were overhydrated intravenously following a standard protocol which included the administration of a saline solution containing Mg sulfate followed by the infusion of mannitol [21]. Renal function before the initiation of chemotherapy was normal in all cases, with the exception of a child who had a mild but persistent renal tubular dysfunction due to the prior administration of ifosfamide [22].

Controls

A control population was formed by 63 children (32 males, 31 females) aged 1–15 years. Age distribution was as follows: 1–4 years, n = 14; 4–10 years, n = 28; 10–15

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years, n = 21. Most data represent follow-up studies in patients referred to the Renal Clinic due to urinary tract infection and were carried out at a time when clinical abnormalities were not already present. All subjects were on a standard, uncontrolled diet and received no medications.

Methods

Biochemical data in all 22 children were retrospectively analyzed to establish its relation with the amount of cisplatin received and the time elapsed since its administration. Data in 10 children in whom hypomagnesemia developed during therapy are analyzed in more detail. In 18 children (2 died and 2 were still treated with cisplatin) we followed renal function prospectively for a mean time of 2.3 years (range: 0.5–5.2 years) after arrest of cisplatin therapy. At the time of the study, 13 children (72%) were free of apparent disease and did not receive any specific treatment.

In 6 patients exhibiting chronic hypomagnesemia despite being off therapy, we analyzed renal tubular reabsorption of Mg following the study protocol proposed by Rude et al. [23] and modified by us for children [24]. Mg was infused as $MgSO_4.7H_2O$ diluted in 5% dextrose in water. A total dose of 49 mEq Mg^{2+}/1.73 m^2 b.s.a. was administered during 180 min and repeat samples of blood and urine were collected at 30-min intervals.

Calcium and Mg were measured by atomic absorption spectrophotometry using a Perkin-Elmer spectrophotometer. An ultrafilterable fraction of plasma Mg (UfMg) was determined by the use of ultrafiltration cones (Centrifree Micropartition System, Amicon Division, Grace & Co., CT) [25]. Creatinine, (Cr) was analyzed using a kinetic approach to the Jaffe reaction by means of a Beckman Cr analyzer.

Fractional excretion of Mg (FE_{Mg}) and fractional excretion of K (FE_K) were calculated as follows, respectively: $U_{Mg} \times P_{Cr}/U_{Cr} \times P_{UfMg}$ and $U_K \times P_{Cr}/U_{Cr} \times P_K$.

Statistical analysis was performed using the Sigma (Horus Hardware, Madrid, Spain) and Statistix 4.0 programs (Analytical Software, St. Paul, MN). Data are presented as mean ± SD. Statistical significance was determined by Student's or analysis of variance (ANOVA) tests. The linear or curvilinear equation with greater significance was selected in the regression analysis. $P < 0.05$ was considered significant.

RESULTS

Acute Effects

The 22 children receiving cisplatin had overall values of plasma Mg and UfMg significantly lower than values found by us in 63 control children: 1.51 ± 0.38 vs. 1.70 ± 0.15 mg/dl, $P < 0.001$; 0.71 ± 0.34 vs. 1.18 ± 0.10 mg/dl, $P < 0.05$, respectively.

Data in 10 patients developing acute hypomagnesemia are presented with more detail. A significant correlation was observed between cumulated dose of cisplatin and plasma Mg concentration ($r = -0.36$, $P < 0.001$). As shown in Figure 1, the plasma Mg concentration attained after each cisplatin dose became progressively lower in each individual patient with repeated doses. ANOVA test also demonstrated that plasma Mg values present after each cisplatin dose were significantly lower ($P < 0.001$) than values present prior to the dose. Hypomagnesemia (plasma Mg < 1.4 mg/dl) was observed when a cumulated dose of 300–750 mg/m^2 b.s.a. of cisplatin was given (mean 500 mg/m^2 b.s.a.). Once hypomagnesemia had developed it reappeared after each therapy cycle in spite of prior normalization of plasma Mg values.

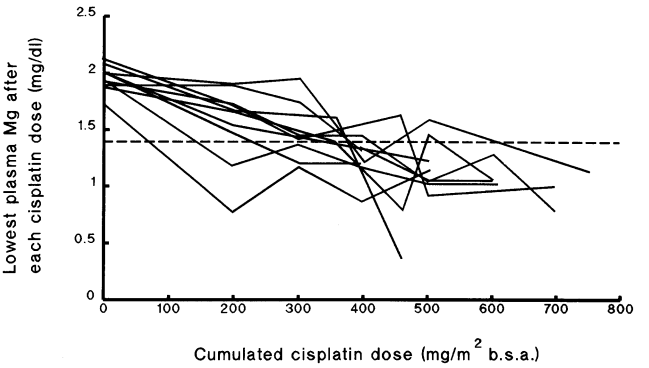

Fig. 1. Relationship between cumulated dosage of cisplatin and plasma Mg values in 10 patients developing hypomagnesemia.

In 2 patients acute hypomagnesemia was already apparent after the first dose of cisplatin (50 mg/m^2 b.s.a.): 1 had received ifosfamide previously and had a mild but persistent proximal tubular dysfunction, and 1 developed acuted renal insufficiency after the first cisplatin dose. These 2 patients were excluded from the statistical analysis relating plasma Mg and cumulated cisplatin dosage. With the exception mentioned, the effect of cisplatin therapy on glomerular function was not very apparent, since in the other patients the mean rise in plasma Cr concentration was only 0.2 mg/dl.

Hypermagnesiuria, both expressed as FE_{Mg} (20.5 ± 18.5 vs. 3.9 ± 1.7%, $P < 0.01$) or urinary Mg to Cr ratio (0.15 ± 0.07 vs. 0.08 ± 0.04 mg/mg, $P < 0.01$), developed in all cases and was especially important immediately after cisplatin treatment. In 10 patients, a significant and inverse correlation could be established between urinary Mg to Cr ratio and the time elapsed since cisplatin administration ($r = -0.37$, $P < 0.001$). Figure 2 depicts the characteristic profile of plasma Mg and urinary Mg to Cr ratio observed in one patient after a cycle of cisplatin therapy. Manifest hypermagnesiuria only persisted for a few days and preceded the appearance of hypomagnesemia, but complete normalization of urine values required more than 1 month. Urinary Mg wasting was accompa-

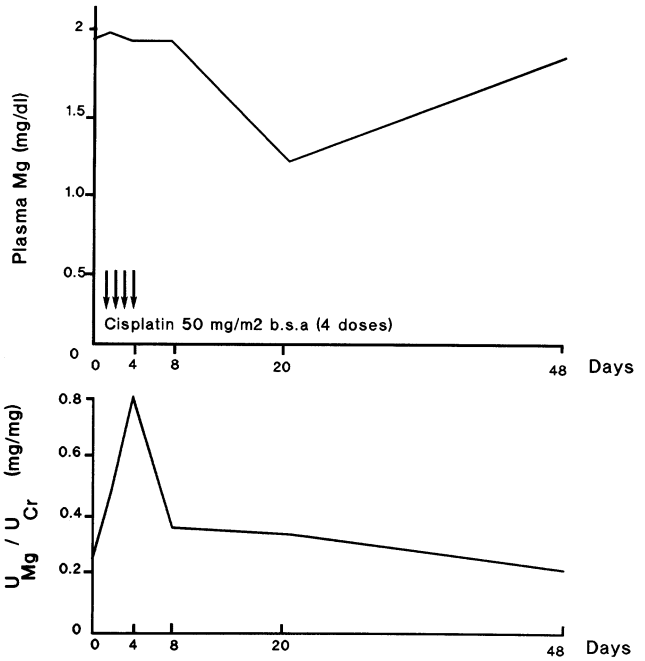

Fig. 2. Representative sequence of plasma and urine Mg values in one patient receiving cisplatin therapy.

nied by polyuria and loss of other electrolytes such as calcium, sodium, and potassium. In fact, urinary Mg to Cr ratio correlated significantly with urinary Ca to Cr ratio ($r = 0.42$), FE_{Na} ($r = 0.60$), and FE_K ($r = 0.59$).

Chronic Effects

In the 18 patients studied and despite that considerable time has passed since the arrest of cisplatin therapy, plasma Mg and UfMg were significantly lower than control values (1.5 ± 0.21 mg/dl, $P < 0.001$; 1.02 ± 0.16 mg/dl, $P < 0.01$, respectively). FE_{Mg} persisted also moderately elevated ($6.8 \pm 4.1\%$, $P < 0.05$). No correlations could be established between plasma Mg and either the amount of cisplatin received or the time elapsed since its administration. In 6 patients (33%), significant hypomagnesemia was still present, with plasma Mg and UfMg values ranging between 1.0–1.4 and 0.7–1.1 mg/dl, respectively (Table I). It is interesting to remark that only 4 of the 6 patients with chronic hypomagnesemia exhibited this finding during cisplatin therapy. Other renal abnormalities detected were moderate elevation of plasma Cr in 6 patients, hypokalemia in 1 patient, and hypocalciuria in 5 patients.

Functional studies in the 6 patients with chronic hypomagnesemia revealed that the characteristics of renal Mg reabsorption were not homogenous. In Figure 3, urinary Mg excretion during Mg sulfate infusion is expressed as milligrams per 100 ml glomerular filtrate (GF) along the ordinate, and the amount filtered, also expressed as milligrams per 100 ml GF, is represented along the abscissa. The point where the excretion line crosses the abscissa gives the value of renal Mg threshold. The Tm of Mg reabsorption is calculated by the vertical distance between the bisector and the excretion line. Patients 1–3 had rates of renal Mg reabsorption similar to or slightly below control values and hypomagnesemia was easily corrected by simple dietary measures. Patients 4–6 exhibited an overall impairment in Mg reabsorption at all levels of filtered Mg, indicating that both renal threshold and Tm were decreased. Patients 5 and 6, presenting the lower rates of Mg reabsorption, were the ones also presenting the more severe acute toxic effects.

The relationship between urinary excretions of Ca and Mg during $MgSO_4$ infusion is depicted in Figure 4. It can be observed that for each value of excreted Mg there are no evident differences in Ca excretion between control and cisplatin-treated children.

DISCUSSION

Acute Effects

The acute effects of cisplatin administration on renal Mg homeostasis are well recognized in the pediatric literature and depend upon the cumulated dose of the drug [4–7,15]. The present investigation clearly demonstrates that the minimal dose required to induce hypomagnesemia was 300 mg/m^2 b.s.a., an amount similar to that previously reported in adults [4,7]. The progressive decrease in plasma Mg was related to the cumulated effect of repeat doses, since its recovery after each therapy cycle was always incomplete [26]. In this study the time elapsed between administration of cisplatin and appearance of hypomagnesemia was approximately 15 days, a time shorter than that observed in adults [4,15]. Once hypomagnesemia had developed it reappeared sooner and sooner after each cisplatin dose [27,28].

The wide variability observed on the toxicity of cisplatin is probably the consequence not only of different patients' sensitivities but also of variations of body Mg stores [6] and of other participating factors [29]. In our study, two children developed early and severe hypomagnesemia after the first dose of cisplatin. In one, a picture of acute renal insufficiency was present [30]; in the other, the toxic effects of cisplatin were added to the toxic effects of ifosfamide [22,31,32].

As shown in the present study, hypomagnesemia resulted from increased urinary losses of Mg [7], which diminished progressively during the days following drug administration [33]. The urinary Mg wasting after cisplatin administration was maintained for several days as a result of the persistence of the drug both in plasma [34,35] and in renal tissue [36]. As characterized in rabbits and rats by micropuncture and microperfusion experiments [37,38], of the filtered amount of Mg, 20–25% is reabsorbed by the proximal tubule, 50–60% is reabsorbed

TABLE I. Patients With Chronic Hypomagnesemia Secondary to Prior Cisplatin Therapy*

				Plasma				Urine			
No.	Age (years)	Sex	Years off therapy	Mg (mg/dl)	UfMg (mg/dl)	K (mEq/l)	Cr (mg/dl)	U_{Mg}/U_{Cr} (mg/mg)	FE_{Mg} (%)	U_{Ca}/U_{Cr} (mg/mg)	FE_K (%)
1	16	F	2.0	1.40	1.15	4.7	0.8	0.03	2.3	0.03	8.4
2	6	F	2.1	1.30	—	3.4	0.6	0.12	—	0.24	14.4
3	3	F	2.2	1.40	1.10	4.0	0.4	0.16	5.9	0.20	9.4
4	5	F	3.9	1.21	0.76	3.6	0.6	0.08	6.0	0.08	19.6
5	13	M	2.5	1.00	0.70	2.3	0.6	0.12	10.6	0.11	9.3
6	13	M	2.5	1.30	0.95	3.8	0.6	0.30	19.3	0.26	26.7
Reference values[a] (mean ± SD)				1.70 ± 0.15	1.18 ± 0.10	4.34 ± 0.47	0.45 ± 0.11	0.08 ± 0.04	3.9 ± 1.7	0.14 ± 0.6	11.5 ± 4.6

*UfMg: ultrafilterable Mg; FE_{Mg} and FE_K: fractional excretion of Mg and fractional excretion of K, respectively.
[a]Data obtained in our laboratory.

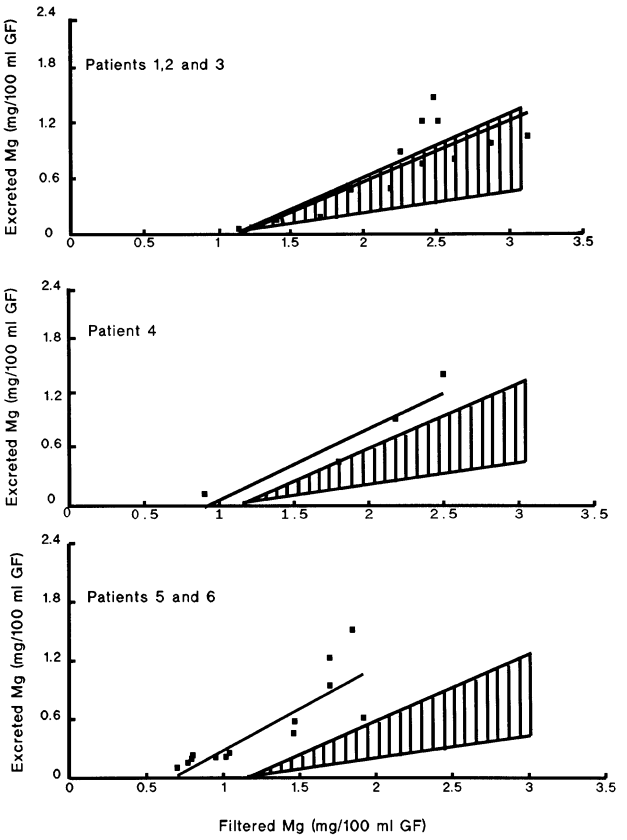

Fig. 3. Urinary Mg excretion during infusion of Mg sulfate is plotted against the filtered Mg load. The hatched area covers the range of values obtained in 6 control children.

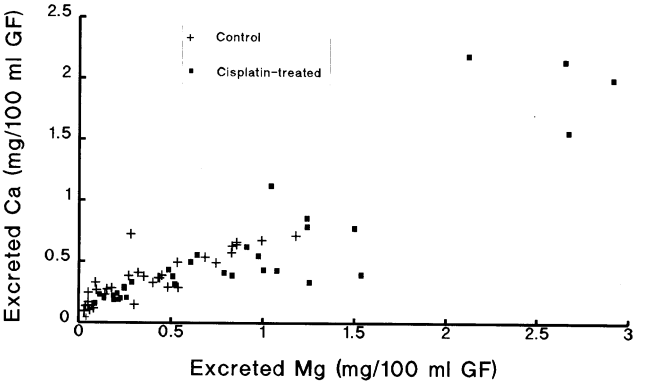

Fig. 4. Relationship between excreted values of Ca and Mg sulfate infusion in both 6 control and 6 cisplatin-treated children.

in the thick ascending limb of Henle, and the remaining 5–10% is reabsorbed in the distal convoluted tubule and collecting ducts. Therefore, the acute toxic effects of cisplatin on renal Mg handling mainly derive from its early and sustained accumulation in renal tubular cells where it induces progressive necrotic damage [39–43]. Renal deposit of cisplatin is already evident within 6 hr after its administration [39] and there is a direct relationship between the amount deposited and the degree of renal tubular damage [36,42,43].

Other renal functional abnormalities observed in the present study such as elevation of plasma Cr, polyuria, and increased urinary losses of electrolytes have been previously recognized [8,9,44,45].

Chronic Effects

Several authors have reported in adults that acute administration of cisplatin is followed by a chronic Mg-losing nephropathy that may persist a long time after withdrawal of therapy [10–13]. This chronic nephropathy may also develop in children [18,20]. In the present series persistent renal function abnormalities were observed in as many as 33% of children previously treated with cisplatin. We could not find any relation between either the cumulated dose given or the time elapsed since its administration and the presence of renal abnormalities. This experience in humans is not surprising since a chronic tubulointerstitial nephropathy also develops in the rat after cisplatin administration [39,46,47].

Renal functional studies in 6 children with chronic hypomagnesemia revealed heterogenous results. In 3 asymptomatic children (cases 1–3), rates of tubular Mg reabsorp-

tion were completely normal and the hypomagnesemia was easily corrected by dietary measures. Either a reduced intake or an impaired intestinal absorption of Mg [41] were probable causes. In the remaining 3 patients the degree of hypomagnesemia was directly related to decreased rates of tubular Mg reabsorption. The 2 children with the lowest plasma Mg values were those exhibiting the lowest rates of tubular Mg reabsorption (patients 5 and 6). Although Mg therapy was greatly ineffective at normalizing plasma Mg values, patient 4 remained asymptomatic with oral Mg therapy while patients 5 and 6 required sustained parenteral administration.

It has been suggested that the chronic hypomagnesemia observed after cisplatin therapy is often accompanied by hypocalciuria, thus mimicking the biochemical features of Gitelman's syndrome [11,20]. This autosomal recessive disorder should be differentiated from classic Bartter's syndrome, in which normo- and hypercalciuria are present [24,48]. Our findings do not support the hypothesis that chronic cisplatin nephropathy represents the acquired counterpart of such inherited disorder. First, the impairment in tubular Mg reabsorption described herein is much greater than that observed in patients with Gitelman's syndrome in whom a low renal Mg threshold but a normal renal Mg Tm are present [24,49]. Second, when patients with Gitelman's syndrome are submitted to a parenteral Mg load they are not capable of a parallel increase in urinary Ca excretion, as observed in normal individuals [50]. However, all 6 patients studied maintained an intact capacity to simultaneously increase the excretion of both cations, a fact also observed in rats with chronic cisplatin nephropathy [41,46].

Chronic cisplatin nephropathy is obviously related to persistent renal tubulointerstitial damage induced by the prior administration of the drug. In contrast to experimental acute renal toxicity, mainly characterized by early and reversible tubular degenerative changes, chronic renal toxicity is histologically manifested in rats by tubulointerstitial damage with development of cysts [46,47]. No similar pathologic studies have been reported in humans. Further clinical and experimental studies are necessary to better understand the initiation and evolution of this chronic nephropathy. Also, future investigations should be designed to better know if different pharmacologic regimes may attenuate the appearance and severity of the chronic renal damage.

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REFERENCES

1. Fillastre JP, Viotte C, Morin JP, Moulin B: Nephrotoxicity of antitumoral agents. Adv Nephrol 17:175–218, 1988.
2. Narins RG, Carley M, Bloom EJ, Harrison DS: The nephrotoxicity of chemotherapeutic agents. Semin Nephrol 10:556–564, 1990.
3. Meyer KB, Madias NE: Cisplatin nephrotoxicity. Miner Electrolyte Metab 20:201–203, 1994.
4. Ashraf M, Scotchel PL, Krall JM, Flink EB: Cisplatinum-induced hypomagnesemia and peripheral neuropathy. Gynecol Oncol 16: 309–318, 1983.
5. Buckley JE, Clark VL, Meyer TJ, Pearlman NW: Hypomagnesemia after cisplatin combination chemotherapy. Arch Intern Med 144:2347–2348, 1984.
6. Stewart AF, Keating T, Schwartz PE: Magnesium homeostasis following chemotherapy with cisplatin: A prospective study. Am J Obstet Gynecol 153:660–665, 1885.
7. Lam M, Adelstein DJ: Hypomagnesemia and renal magnesium wasting in patients treated with cisplatin. Am J Kidney Dis 7:164–169, 1986.
8. Rodrıguez M, Solanki DL, Whang R: Refractory potassium repletion due to cisplatin-induced magnesium depletion. Arch Intern Med 149:2592–2594, 1989.
9. Lyman NW, Hemelatha C, Viscuso RL, Jacobs MG: Cisplatin-induced hypocalcemia and hypomagnesemia. Arch Intern Med 140:1513–1514, 1980.
10. Schilsky RL, Barlock A, Ozols RF: Persistent hypomagnesemia following cisplatin chemotherapy for testicular cancer. Cancer Treat Res 66:1767–1769, 1982.
11. Mavichak V, Coppin CML, Wong NLM, Dirks J, Walker VR, Sutton RAL: Renal magnesium wasting and hypocalciuria in chronic cisplatinum nephropathy in man. Clin Sci 75:203–207, 1988.
12. Sutton RAL, Walker VR, Halabe A, Swenerton K, Coppin CML: Chronic hypomagnesemia caused by cisplatin: Effect of calcitriol. J Lab Clin Med 117:40–43, 1991.
13. Brillet G, Deray A, Jacquiaud C, Mignot L, Bunker D, Meillet D, Raymond F, Jacobs C: Long-term effect of cisplatin in man. Am J Nephrol 14:81–84, 1994.
14. Hill JB, Blachley JD, Trotter M: Hypomagnesemia, hypocalcemia and hypokalemia with cis-platinum therapy. Clin Res 26:780A, 1978.
15. Schilsky RL, Andersen T: Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. Ann Intern Med 90:929–931, 1979.
16. Womer MW, Pritchard J, Barratt TM: Renal toxicity of cisplatinum in children. J Pediatr 106:659–663, 1985.
17. Welch RJ, Pearson AD, Craft AW: Tetany in children with cisplatinum. Pediatr Hematol Oncol 4:167–170, 1987.
18. Brock PR, Koliouskas DE, Barratt TM, Yeomans E, Pritchard J: Partial reversibility of cisplatin nephrotoxicity in children. J Pediatr 118:531–534, 1991.
19. Kibirige MS, Morris-Jones PH, Addison GM: Prevention of cisplatin-induced hypomagnesemia. Pediatr Hematol Oncol 5:1–6, 1988.
20. Bianchetti Mg, Kanaka C, Ridolfi-Luthy A, Wagner HP, Hirt A, Paunier L, Peheim E, Oetliker OH: Chronic renal magnesium loss, hypocalciuria and mild hypokalaemic metabolic alkalosis after cisplatin. Pediatr Nephrol 4:219–222, 1990.
21. Rosen G, Nirenberg A, Caparros B: Cisplatinum in metastatic osteogenic sarcoma. In Prestayko AW, Crooke ST, Carter SK (eds): "Cisplatin: Current Status and Developments." New York: Academic Press, 1980, pp 465–475.
22. Navajas A, Vallo A, Labayru T, Moya E: Renal toxicity (Fanconi's syndrome) due to ifosfamide therapy. Med Pediatr Oncol 17:331, 1989.
23. Rude RK, Bethune JE, Singer FR: Renal tubular maximum for magnesium in normal, hyperparathyroid and hypoparathyroid man. J Clin Endocrinol Metab 51:1425–1431, 1980.
24. Rodrıguez-Soriano J, Vallo A, Garcıa-Fuentes M: Hypomagnesemia of hereditary renal origin. Pediatr Nephrol 1:465–472, 1987.
25. D'Costa M, Cheng P: Evaluation of the amicon MPS-1 system for the measurement of ultrafilterable serum calcium and magnesium. Clin Chem 27:1057, 1981.

26. Sartori S, Nielsen I, Tassinari D, Rigolin F, Arcudi D, Abbasciano V: Changes in intracellular magnesium concentrations during cisplatin chemotherapy. Oncology 50:230–234, 1993.
27. Vogelzang NJ, Torkelson JL, Kennedy BJ: Hypomagnesemia, renal dysfunction and Raynaud's phenomenon on patients treated with cisplatin, vinblastine and bleomycin. Cancer 56:2760–2770, 1985.
28. Miller JM: Prophylactic hypomagnesemia during cisplatin therapy. Arch Intern Med 145:2270, 1985.
29. Flombaum CD: Hypomagnesemia associated with cisplatin combination chemotherapy. Arch Intern Med 144:2336–2337, 1984.
30. Gomez-Campdera FJ, Gonzalez P, Carrillo MA, Estelles MC, Rengel M: Cisplatin nephrotoxicity: Symptomatic hypomagnesaemia and renal failure. Int J Pediatr Nephrol 7:151–152, 1986.
31. Caron HN, Abeling N, Gennip A van, Kraker J de, Voute PA: Hyperaminoaciduria identifies patients at risk of development of renal tubular toxicity associated with ifosfamide and platinate containing regimes. Med Pediatr Oncol 20:42–47, 1992.
32. Rossi RM, Kist C, Wurster U, Kulpmann WR, Ehrich JHH: Estimation of ifosfamide/cisplatinum-induced renal toxicity by urinary protein analysis. Pediatr Nephrol 8:151–156, 1994.
33. Abbasciano V, Mazzotta D, Vecchiatti G, Tassanari D, Nielsen I, Sartori S: Changes in serum, erythrocyte and urinary magnesium after a single dose of cisplatin combination chemotherapy. Magnesium Res 4:123–125, 1991.
34. Litterst CL, Gram TE, Dedrick RL, Leroy AF, Guarino AM: Distribution and disposition of platinum following intravenous administration of cis-diamminedichloroplatinum II to dogs. Cancer Res 36:2340–2344, 1976.
35. Lagasse LD, Pretorius RG, Ford LC, Hoescheke J, Kean C: The metabolism of cis-dichlorodiammineplatinum II: Distribution, clearance and toxicity. Am J Obstet Gynecol 139:791–798, 1981.
36. Safirstein R, Miller P, Guttenplan JB: Uptake and metabolism of cisplatin by rat kidney. Kidney Int 25:753–758, 1984.
37. Sutton RAL, Dirks JH: Calcium and magnesium: Renal handling and disorders of metabolism. In Brenner BM, Rector FC Jr (eds): "The Kidney." 3rd Ed. Philadelphia: W.B. Saunders, 1986 pp 551–618.
38. De Rouffignac C, Quamme GA: Renal magnesium handling and its hormonal control. Physiol Rev 74:305–322, 1994.
39. Choie DD, Longnecker DS, Del Campo A: Acute and chronic cisplatin nephropathy in rats. Lab Invest 44:398–402, 1981.
40. Chopra S, Kaufman JS, Jones TW, Hong WK, Gehr MK, Hamburger RJ, Flamenbaum W, Trump BJ: Cis-diamminedichloroplatinum-induced acute renal failure in the rat. Kidney Int 21:54–64, 1982.
41. Mavichak V, Wong NLM, Quamme GA, Magil AB, Sutton RAL, Dirks JH: Studies on the pathogenesis of cisplatin-induced hypomagnesemia in rats. Kidney Int 28:914–921, 1985.
42. Magil AB, Mavichak V, Wong NLM, Quamme A, Dirks JH, Sutton RAL: Long-term morphological and biochemical observations in cisplatin-induced hypomagnesemia in rats. Nephron 43:223–230, 1986.
43. Jongejan HTM, Provoost AP, Wolffe ED, Molenaar JC: Nephrotoxicity of cisplatin comparing young and adults rats. Pediatr Res 20:9–14, 1986.
44. Hutchinson FN, Perez EA, Gandara JR, Lawrence HJ, Kaysen GA: Renal salt wasting in patients treated with cisplatin. Ann Intern Med 108:21–25, 1988.
45. Wong NL, Walker VR, Wong EF, Sutton RA: Mechanism of polyuria after cisplatin therapy. Nephron 65:623–627, 1993.
46. Goldstein MH, Safirstein R, Churg J: Chronic tubulo-interstitial disease after repeated doses of cisplatin. Kidney Int 19:201, 1981.
47. Brillet G, Deray G, Dubois M, Beaufils H, Maksud P, Bourbouze R, Jouanneau C, Jacobs C: Chronic cisplatin nephropathy in rats. Nephrol Dial Transplant 8:206–212, 1993.
48. Betinelli A, Bianchetti MG, Girardin E, Caringella A, Cecconi M, Claris Appiani A, Pavanello L, Gastaldi R, Isimbaldi C, Lama G, Marchesoni C, Matteuchi C, Patriarca P, Di Natale B, Setzw C, Vitucci P: Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. J Pediatr 120:38–43, 1992.
49. Sutton RAL, Mavichak V, Halabe A, Wilkins GE: Bartter's syndrome: Evidence suggesting a distal tubular defect in a hypocalciuric variant of the syndrome. Miner Electrolyte Metab 18:43–51, 1992.
50. Shafik IM, Green G: Effect of magnesium on renal calcium excretion. Kidney Int 31:357, 1987.
51. Ariceta G, Navajas A, Astigarraga I, Fernandez-Tejeiro A, Vallo A, Rodrıguez-Soriano J: Magnesium losing nephropathy due to cisplatin. Med Pediatr Oncol 23:292, 1994.